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LGE and NT-proBNP Identify Low Risk of Death or Arrhythmic Events in Patients With Primary Prevention ICDs

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OBJECTIVES The aim of this study was to investigate whether late gadolinium enhancement (LGE) magnetic resonance imaging or N-terminal pro–B-type natriuretic peptide (NT-proBNP) could identify patients with a low risk of death or use of implantable cardioverter-defibrillator (ICD) in patients receiving a primary prevention ICD.

BACKGROUND ICDs reduce mortality in patients with heart failure (HF), although two-thirds may never use their device. Current risk stratification, based on New York Heart Association functional class and left ventricular ejection fraction, still leads to implantation of ICDs in patients who may never need their device.

METHODS We examined 157 patients with HF (61 with ischemic cardiomyopathy and 96 with dilated cardiomyopathy; mean age 50.5 years; 78% male) who underwent primary prevention defibrillator implantation. Presence and volume of LGE was measured before device implantation, and serum NT-proBNP level was measured before ICD implantation. The combined primary endpoint was cardiovascular death or appropriate ICD therapy (either appropriate shock or antitachycardia pacing).

RESULTS The primary outcome occurred in 32 patients (20.4%) over a median follow-up period of 915 days. Percentage of LGE (hazard ratio [HR]: per 1% increase: 1.06; 95% confidence interval [CI]: 1.04 to 1.09; $p < 0.001$) and (ln) NT-proBNP (HR: 1.44; 95% CI: 1.04 to 1.98; $p = 0.027$) were predictors of death or appropriate ICD activation and remained significant when entered into multivariable analysis. When the cohort was stratified into tertiles based on LGE percentage and NT-proBNP, we were able to identify a low-risk group (event rate 3% per year, compared with the intermediate- and high-risk groups [6% and 10% per year, respectively]).

CONCLUSIONS Both percentage of LGE and NT-proBNP were associated with higher risk of death or appropriate ICD activation. The use of these markers in combination may be useful in identifying individuals most likely to benefit from this costly intervention, and more specifically, in the identification of a group at lower risk in whom ICD implantation may be deferred. (J Am Coll Cardiol Img 2014;7:561–9)

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Implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy devices with a defibrillator function (CRT-Ds) have been shown to reduce mortality when implanted to prevent death in patients with heart failure (HF) who have not had a prior cardiac arrest (i.e., a primary prevention device) (1,2). The average annual rate of appropriate shocks in clinical trials is only 5.1%, and as many as two-thirds of patients may never use their ICD after implantation (2–4). Therefore, methods to improve the identification of individuals who may not be likely to benefit from ICD implantation meeting conventional criteria such as New York Heart Association (NYHA) functional class II to IV and reduced ejection fraction are needed.

Late gadolinium enhancement (LGE) by cardiac magnetic resonance (CMR) has been proposed as a potential marker of risk identifying individuals most likely to benefit from an ICD. The presence of LGE is associated with a higher risk of all-cause mortality, sudden cardiac death, appropriate ICD activation, and admissions for heart failure in patients with HF with both ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) (5–11). However, LGE quantification has a number of limitations; furthermore, not all patients are able to undergo CMR due to relative or absolute contraindications or due to a contraindication to the administration of gadolinium.

ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy (device with) defibrillator

DCM = dilated cardiomyopathy

HF = heart failure

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

LGE = late gadolinium enhancement

NT-proBNP = N-terminal pro–B-type natriuretic peptide

In contrast, B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are easily measured and have been explored as a potential marker of risk in those receiving a primary prevention ICD and as predictors of sudden death in patients with HF (12–14). We assessed the association between LGE and NT-proBNP and death or appropriate ICD activation in individuals undergoing implantation of a primary prevention ICD, and specifically, hypothesized that the 2 markers may be combined to predict a group of patients who may be at low risk of ventricular arrhythmia and ICD activation.

METHODS

Patient selection. We prospectively evaluated 157 consecutive patients referred to our tertiary center for implantation of primary prevention ICD or CRT-D between January 2008 and December 2010. Patients with both ICM and nonischemic DCM were included. The diagnosis of ICM was made using either computed tomography (CT) coronary angiography or invasive coronary angiography in conjunction with CMR results. If patients were found to have a small area of LGE in an ischemic distribution that was thought not to be significant enough to cause the degree of left ventricular systolic impairment seen they were classified as DCM; conversely, in some patients, there was a definite regional wall motion abnormality in conjunction with a history of significant stenosis on invasive or CT coronary angiography (>70%), and we recorded these patients as having ICM. We excluded all patients referred for a secondary prevention ICD and those with renal impairment (estimated glomerular filtration rate <30 ml/min/1.73 m^2). The West of Scotland Research Ethics Committee approved the study.

CMR protocol. All patients underwent a clinically indicated CMR examination with a 1.5-T scanner (Avanto Siemens, Erlangen, Germany). The protocols, imaging sequences, and analysis have been previously described (15). Briefly, cine images were obtained using a steady-state free precession sequence in 3 long-axis planes (2-, 3-, and 4-chamber) and in short-axis slices through the left ventricle (echo time/repetition time/flip angle 1.4/3.5/50; spatial resolution 1.7 × 2 mm; slice thickness 8 mm). LGE imaging for myocardial infarction was acquired 10 min (after a total accumulative gadolinium–diethylene triamine pentaacetic acid of 0.15 mmol/kg) by an inversion recovery fast gradient echo sequence. Inversion time was adjusted to null normal myocardium—typically this was between 280 and 320 ms. CMR was carried out within a mean of 3 ± 1 days of defibrillator insertion.

All analyses were performed using commercially available proprietary software (Argus, Siemens). Left ventricular diameter, volumes, and function were derived from the short-axis slices using manual tracing of the endocardial contours, including papillary muscles as part of the ventricular volume. The presence of LGE was assessed by identification of areas of myocardium with a signal intensity of >5 SD above normal myocardium. Quantification of LGE was measured using manual planimetry in short axis and taking this area as a percentage of the total left ventricular area measured in short axis.

NT-proBNP sampling. Serum NT-proBNP was obtained within 2 ± 1 weeks of defibrillator implantation and analyzed in our local laboratory, the methods for which have been previously described (16). Blood samples were collected in ethylenediamine–tetraacetic acid–containing tubes before being centrifuged at 3,000 rpm for 10 min at

0°C before measurement of NT-proBNP using a chemiluminescent immunoassay kit (Roche Diagnostics, Basel, Switzerland) on an Elecsys 2010 analyzer (Roche Diagnostics). Normal values in our laboratory are <125 pg/ml in patients <75 years of age and <450 pg/ml in patients >75 years of age. All participants were stable outpatients, and hemodynamic status at the time of sampling was similar to status at the time of CMR.

ICD implantation. All patients had an ICD or CRT-D device implanted using standard techniques. Choice of device was at the discretion of the operator. Following implantation defibrillation threshold, testing was carried out in all cases to ensure an appropriate safety margin for device programming.

Clinical follow-up. The pre-defined primary outcome was death or appropriate ICD therapy (either shock for ventricular fibrillation/tachycardia or antitachycardia pacing for ventricular tachycardia [VT]). All patients were followed up at 3- to 6-month intervals using computerized record linkage for death and admissions for ventricular arrhythmias causing appropriate ICD activation. Further information about appropriate ICD activation not causing hospital admission was obtained by searching the records of routine local hospital ICD interrogations. The interrogations occur every 6 months unless the patient experiences a potential ICD activation, in which case the ICD is interrogated after a patient reports the potential event. An independent observer blinded to the CMR analysis and NT-proBNP results adjudicated events (N.T.). No patients were lost to follow-up.

Statistical analysis. Continuous variables are expressed as mean ± SD (median and interquartile range when appropriate), and categorical variables are expressed as n (%). Differences between groups were tested using Student *t* tests or chi-square tests as appropriate. Because the distribution of NT-proBNP was skewed, it was log-transformed, and geometric means were calculated. Kaplan-Meier and Cox proportional hazards survival analysis was used to examine the association between LGE and NT-proBNP (and a number of other baseline variables) and the outcome of death or ICD activation. Percentage LGE and NT-proBNP were most strongly associated with the outcome as assessed by the chi-square statistic and were explored further. Due to the relatively modest number of events, the multivariable model included only significant univariable predictors of the primary outcome ($p < 0.05$ in univariable Cox regression analysis). The type of device (ICD vs. CRT-D) was also included to try to adjust for the mortality and morbidity benefits of CRT (17). Correlation between percentage LGE and NT-proBNP was assessed using the Pearson correlation coefficient. Finally, to evaluate the optimal discriminatory level of percentage LGE and NT-proBNP for identification of a population at low risk of death or ventricular arrhythmia, we divided both DCM and ICM groups into tertiles based on percentage LGE and NT-proBNP. Patients with percentage LGE and NT-proBNP in the lowest tertile for their respective group were selected as the lowest-risk category, whereas all other patients were judged high risk. Intraobserver and interobserver variability is as previously described in our group (15). For all analyses, a p value <0.05 was considered statistically significant, and all p values are 2-tailed. SPSS version 19.0 was used (IBM, Armonk, New York).

RESULTS

A total of 157 patients were included, 60 with ICM and 97 with DCM. Baseline characteristics of each group are summarized in Table 1. Differences between the groups were as expected—the ICM cohort was older with more smokers and with patients more likely to have undergone prior revascularization. The ICM group was more likely to have LGE on CMR and a higher mean volume of fibrosis measured as percentage LGE (24.8% vs. 2.1%, respectively, for ICM vs. DCM patients; $p < 0.001$). The use of evidence-based therapy for HF was high in both groups (total on beta-blockers 82.2%, angiotensin-converting enzyme inhibitors 82.2%, and spironolactone 58.9%). As would be expected, the majority of patients had mild to moderately symptomatic HF (86.6% NYHA functional class II to III) and low ejection fraction by CMR.

Median follow-up for patients without the primary outcome was 915 days. During the follow-up period, 32 patients (20.4%) died or had appropriate ICD therapy (either shock for ventricular fibrillation/tachycardia or antitachycardia pacing for sustained VT). There were 12 cardiac deaths (10 due to end-stage HF and 2 due to myocardial infarction), 14 appropriate defibrillator shocks, and 6 episodes of appropriate antitachycardia pacing. The differences between the groups stratified by outcome are summarized in Table 2. Patients who experienced the primary outcome were more likely to have ICM and LGE on CMR and overall had a higher mean percentage LGE (18.8% vs. 7.4%; $p = 0.01$). The patients who experienced the

Table 1. Baseline Clinical and CMR Characteristics of the Cohort Stratified by Etiology

	Dilated Cardiomyopathy (n = 96)	Ischemic Cardiomyopathy (n = 61)	p Value
Clinical			
Age, yrs	46.0 ± 13.4	57.7 ± 11.2	<0.001
Male	75 (78.1)	48 (78.6)	0.69
AF	18 (18.8)	17 (27.9)	0.15
Hypertension	14 (14.6)	13 (21.3)	0.24
Smoker	19 (19.8)	23 (37.7)	0.010
Diabetes	6 (6.3)	8 (13.1)	0.13
Prior revascularization	6 (6.3)	32 (52.5)	<0.001
LBBB	32 (33.3)	19 (31.1)	0.86
NYHA functional class			
I	15 (15.6)	0 (0.0)	0.006
II	38 (39.6)	24 (39.3)	
III	38 (39.6)	36 (59.0)	
IV	5 (5.2)	1 (1.6)	
Medications			
ACEI/ARB	75 (78.1)	54 (88.5)	0.044
Beta-blocker	79 (86.8)	50 (82.0)	0.76
Spironolactone	46 (47.9)	46 (75.4)	<0.001
Furosemide	52 (54.2)	45 (73.8)	0.007
Digoxin	13 (13.5)	6 (9.8)	0.52
Investigations			
ln NT-proBNP	7.06 ± 1.24	7.46 ± 1.05	0.018
Median NT-proBNP, pg/ml	1,568.0 (363.0–2,760.5)	2,023.0 (576.0–4,779.0)	0.09
CMR variables			
LGE present	24 (25)	61 (100)	<0.001
LGE, %	2.1 ± 6.0	24.8 ± 16.2	<0.001
CMR LV end-diastolic diameter, cm	6.9 ± 2.0	6.7 ± 1.5	0.65
CMR LVEF, %	27.2 ± 16.3	28.5 ± 12.9	0.71

Values are mean ± SD, n (%), or median (interquartile range).
ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CMR = cardiac magnetic resonance; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association.

primary outcome also had a higher median NT-proBNP level (4,153 pg/ml vs. 1,568 pg/ml; p = 0.012).

Patient characteristics associated with the primary outcome in a univariable analysis are summarized in Table 3. The primary outcome occurred in 7 patients with no LGE—there were 3 deaths due to end-stage HF and 4 episodes of appropriate ICD activation. Ischemic etiology (hazard ratio [HR]: 2.42; 95% confidence interval [CI]: 1.19 to 4.9; p = 0.015), presence of LGE (HR: 3.77; 95% CI: 1.48 to 9.58; p = 0.005), and percentage LGE (HR per 1% increase: 1.05; 95% CI: 1.02 to 1.07; p < 0.001) were all associated with the primary outcome. ln NT-proBNP was also a significant predictor of the primary outcome (HR: 1.71; 95% CI: 1.22 to 2.39; p = 0.002). Percentage LGE, ln NT-proBNP, and etiology of cardiomyopathy (ICM or DCM) were entered into the multivariable model, with adjustment for device type (ICD or CRT-D). Both percentage LGE (HR: 1.04; 95% CI: 1.02 to 1.07; p = 0.001) and ln NT-proBNP (HR: 1.69; 95% CI: 1.15 to 2.47; p = 0.007) remained significant predictors of the primary outcome (Table 4).

There was no significant correlation between LGE and ln NT-proBNP (Pearson correlation coefficient 0.14; p = 0.22). Based on the combination of percentage LGE and NT-proBNP, we were able to stratify the cohort into 2 groups as follows: low risk (DCM: n = 20, LGE 0%, NT-proBNP <545 pg/m; ICM: n = 11, LGE <23%, NT-proBNP <898 pg/ml) and high risk (DCM: n = 76, LGE >0%, NT-proBNP ≥545 pg/ml; ICM: n = 50, LGE ≥23%, NT-proBNP ≥898 pg/ml) (Table 5). There was no significant difference in etiology in the composition of the 2 groups (p = 0.67). The primary outcome occurred in 1 of the patients (3%) in the low-risk group, giving an event rate of 1.5% per year, in comparison with the primary outcome occurring in 31 (24.6%) of the high-risk group (event rate 12.3% per year) (Table 5). With the low-risk group as the reference, patients in the high-risk group had a higher risk of death or appropriate ICD activation (high-risk group HR: 9.12; 95% CI: 1.24 to 66.82; p = 0.03) (Table 5 and Fig. 1A). This trend remained consistent when the cohort was broken down into individual etiologies (p = 0.008) (Online Fig. 1).

Secondary outcome: appropriate ICD activation. Appropriate ICD shock or antitachycardia pacing for VT occurred in 20 patients. Both percentage LGE (HR: 1.04; 95% CI: 1.01 to 1.07; p = 0.004) and ln NT-proBNP (HR: 1.81; 95% CI: 1.09 to 3.03; p = 0.023) remained multivariable predictors of outcome (Table 4). Patients not in the low-risk group had a higher risk of the appropriate ICD activation (Fig. 1B). Again, the high-risk group had poorer survival when the etiologies were separated (p = 0.018) (Online Fig. 2). Only 1 patient in the low-risk group had an appropriate ICD activation over the follow-up period, an event rate of 1% per year, in comparison with the high-risk group, who had an event rate of 10.1% per year.

DISCUSSION

In one of the largest studies to date of patients undergoing implantation of an ICD or CRT-D, we found a number of important associations with death or appropriate use of the defibrillators. LGE and NT-proBNP can be used to predict adverse cardiac outcomes in patients with ICDs. The increasing burden of myocardial fibrosis (scar) as measured by percentage LGE was associated with death or appropriate ICD activation independent of etiology of HF (ICM or DCM). Finally, our study is the first to show that in primary prevention patients, the volume of LGE and NT-proBNP can be combined to provide incremental information on risk stratification, identifying a population at significantly increased risk of adverse cardiovascular outcome and a population at lower risk of adverse outcome in whom ICD implantation may not be mandatory.

The presence of LGE on CMR identifies areas of myocardial scar and fibrosis. The link between the pathological presence of scar and fibrosis and ventricular arrhythmias leading to sudden death is well established, caused by the presence of an arrhythmogenic substrate (5,18). Several recent studies have identified the utility of LGE to predict ICD activation in both ICM (9,19–21) and DCM (10). Our study not only corroborated the preceding evidence that the presence of LGE confers an increased risk of adverse outcome but further adds that risk increases in proportion with the volume of LGE and that this is more important than the presence of LGE alone. Two small studies have reported that scar size is associated with adverse outcome in patients with ICM (9,21). Gao et al. (6) studied 124 patients with ICM and DCM and reported that LGE mass was the most significant univariate predictor of the primary combined outcome (ICD activation, sudden death, or survived cardiac arrest), although they did not test this in a multivariable model. We have demonstrated in a larger cohort that this association persists after adjustment for the etiology of the cardiomyopathy and NT-proBNP, which is a consistently strong marker of prognosis in HF (22). A small retrospective study by Scott et al. (9) also described a similar relationship in 64 patients with ICM.

NT-proBNP is secreted by the ventricles in response to increased cardiomyocyte stretch caused by pressure and volume overload (22). It has been shown to be useful as both a diagnostic and a prognostic marker in HF (23–25). Several studies have also examined its utility in predicting adverse outcomes in patients with ICDs. A meta-analysis by Scott et al. (26) identified 8 studies (enrolling a total of 1,047 patients) and found that NT-proBNP (or BNP) levels above the study median increased risk of occurrence of death or ventricular arrhythmia in those with or without an ICD. Another large study by Verma et al. (27) evaluated 345 consecutive patients undergoing primary or secondary prevention ICD implantation and found that BNP was the only significant multivariable predictor of death or appropriate ICD activation. Finally, in a large Italian multicenter study, Biasucci et al. (13) evaluated 300 patients with ICM undergoing primary prevention ICD implantation. In this study, the researchers' primary hypothesis was the use of C-reactive protein as a marker of risk; however, they also found that NT-proBNP levels above the median was a significant predictor of sudden cardiac

Table 2. Clinical and CMR Characteristics Stratified According to Occurrence of the Primary Outcome (Death or Appropriate ICD Activation)

	Primary Outcome (n = 32)	Without Primary Outcome (n = 125)	p Value
Clinical			
Age, yrs	51.6 ± 16.8	50.2 ± 13.2	0.64
Male	27 (84.4)	96 (76.8)	0.35
ICM	18 (56.2)	43 (34.4)	0.024
Diabetes	5 (16.7)	9 (7.1)	0.058
LBBB	8 (26.7)	43 (33.9)	0.84
NYHA functional class			
I	1 (3.1)	14 (11.2)	0.11
II	19 (59.4)	43 (34.4)	
III	11 (34.4)	63 (50.4)	
IV	1 (3.1)	5 (4.0)	
Medications			
ACEI/ARB	18 (60.0)	111 (87.4)	0.059
Beta-blocker	18 (60.0)	111 (87.4)	0.001
Spironolactone	13 (43.3)	79 (62.2)	0.33
Investigations			
ln NT-proBNP	7.79 ± 1.09	7.02 ± 1.19	0.005
NT-proBNP, pg/ml	4,153.0 (1,116.5–5,943.0)	1,568.0 (494.0–2,864.0)	0.012
CMR variables			
Presence of LGE	19 (59.3)	53 (42.4)	0.015
LGE, %	18.8 ± 17.7	7.4 ± 13.4	0.01
CMR LVEF, %	26.2 ± 12.8	27.9 ± 12.8	0.67

Values are mean ± SD, n (%), or median (interquartile range).
ICD = implantable cardioverter-defibrillator; ICM = ischemic cardiomyopathy; other abbreviations as in Table 1.

Table 3. HR and 95% CI for the Association Between Clinical and CMR Characteristics and Death or ICD Activation

	Death/Appropriate ICD Activation (n = 32)		Appropriate ICD Activation (n = 20)	
	Univariable HR* (95% CI)	p Value	Univariable HR* (95% CI)	p Value
Clinical				
Age	1.02 (0.99–1.04)	0.26	1.02 (0.99–1.05)	0.21
Male	1.27 (0.48–3.37)	0.64	0.79 (0.25–2.52)	0.70
ICM	2.42 (1.19–4.90)	0.015	2.63 (1.07–6.50)	0.035
Diabetes	2.14 (0.82–5.58)	0.12	2.75 (0.91–8.29)	0.07
LBBB	1.46 (0.64–3.31)	0.37	1.98 (0.72–5.45)	0.19
NYHA functional class III–IV	2.33 (0.92–5.93)	0.08	3.03 (0.82–11.17)	0.10
Medications				
ACEI/ARB	0.82 (0.36–1.87)	0.64	1.58 (0.47–5.28)	0.46
Beta-blocker	0.53 (0.25–1.13)	0.10	0.66 (0.24–1.82)	0.42
Spironolactone	1.06 (0.51–2.20)	0.87	2.97 (1.01–8.72)	0.047
Investigations				
ln NT-proBNP	1.71 (1.22–2.39)	0.002	1.84 (1.17–2.88)	0.008
CMR variables				
Presence of LGE	3.77 (1.48–9.58)	0.005	3.30 (1.05–10.42)	0.042
LGE, per 1% increase	1.05 (1.02–1.07)	<0.001	1.05 (1.02–1.08)	0.002
CMR LVEF, %	1.00 (0.97–1.03)	0.73	1.01 (0.98–1.05)	0.50

*Adjusted for device type (ICD or cardiac resynchronization therapy [device with] defibrillator).
CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

death and ventricular arrhythmias. Nevertheless, the combined use of NT-proBNP and percentage LGE has not been prospectively evaluated in 1 cohort before.

We hypothesized that because percentage LGE and NT-proBNP are markers of different pathological processes in this group, they may have a differential association with death or ICD activation. We found that they were both strong predictors of risk in this group of patients and that their combination provided additional prognostic information. To the best of our knowledge, this is the first study to demonstrate that both markers were able to identify a group of patients at higher risk of adverse outcomes and that the association was present in a cohort of patients with ICM and DCM. Perhaps of more clinical relevance, the 2 can also be combined to identify a group of patients at low risk of events who might not benefit from ICD implantation. This may be important given the social and psychological implications of a defibrillator and an estimated complication incidence of 4% (28).

Several studies have evaluated the prognostic value of LGE and NT-proBNP individually. Recently, a study by Wu et al. (29) demonstrated the incremental prognostic utility of a combination of imaging and biomarker in patients with chronic HF for prediction of death and arrhythmic events. In this study, the researchers found that the combination of LGE and C-reactive protein was able to identify a cohort at very low risk of adverse cardiovascular outcome. Interestingly, the researchers also noted that patients with the primary outcome had higher NT-proBNP levels, although they did not explore this further. We have demonstrated for the first time that even after adjustment for the presence of each other, percentage LGE and NT-proBNP levels were still associated with adverse outcomes. This is particularly important given the wider availability of serum NT-proBNP testing and its ease of use and interpretation compared with CMR, which is a more specialized tool. Importantly, the primary outcome occurred in 11 patients without LGE, 37% of the total number. Therefore, although LGE appears to be an important predictor of adverse outcome, this finding highlights the value of a multimarker model of risk. Furthermore, it may be of benefit in patients unable to undergo CMR, for example in those with contrast allergy or renal impairment. Of course, in centers with access to CMR, the combination of these 2 markers provides even more predictive confidence. There may also be advantages to identifying a group of lower-risk patients in which the clinician is unsure of proceeding to ICD insertion, perhaps for example in those with ejection fractions around 35% and in NYHA functional class I/II. Ejection fraction can fluctuate over time, whereas NYHA functional class can be fairly subjective. These factors may account for some of the current reduced cost effectiveness of ICDs. There is an increasing recognition, however, that risk stratification for ICD implantation may be further refined by using other markers such as LGE and NT-proBNP;

Table 4. Multivariable Analysis for the Prediction of Death or Appropriate ICD Activation

	Death/Appropriate ICD Activation (n = 32)		Appropriate ICD Activation (n = 20)	
	Multivariable HR* (95% CI)	p Value	Multivariable HR* (95% CI)	p Value
LGE, per 1% increase	1.04 (1.01–1.07)	0.001	1.04 (1.01–1.07)	0.004
Log NT-proBNP	1.69 (1.15–2.47)	0.007	1.81 (1.09–3.03)	0.023
ICM	1.01 (0.32–3.16)	0.99	1.39 (0.33–5.89)	0.66

*Adjusted for device type (ICD or cardiac resynchronization therapy [device with] defibrillator).
Abbreviations as in Tables 1 and 2.

Table 5. Association Between Optimal Discriminatory Level of LGE and NT-proBNP and Death or ICD Activation

Group	Etiology	LGE, %	NT-proBNP (pg/ml)	Number of Patients	Death/Appropriate ICD Activation (%)	Appropriate ICD Activation
Low risk	DCM	0	<545	20 (20.8)	1 (3.1)	0 (0.0)
	ICM	<23	<898	11 (18.0)		
High risk	DCM	>0	≥545	76 (79.2)	31 (24.6)*	20 (15.9)*
	ICM	≥23	≥898	50 (82.0)		

*p < 0.05 compared with low-risk group.
Abbreviations as in Tables 1 and 2.

hence, more studies of this type are required to optimize patient selection and improve outcomes.

Study limitations. Although our sample size and number of events were relatively small and the study was conducted in a single center, our cohort of 157 patients is one of the largest to date of patients undergoing primary prevention defibrillator implantation, CMR examination, and measurement of NT-proBNP. Nevertheless, a larger multicenter study is needed to validate our findings. The overall death rate in our cohort (8.3%) was lower than that reported in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) study (14.2% in 20 months), whereas our rate of appropriate ICD therapies was also lower than that in larger multicenter trials (1,30). Larger studies are needed to find the optimal cutoff points for these markers to be used as risk stratifiers to avoid ICD implantation. These would also allow the incorporation of other variables that may be clinically important.

We used a threshold of >5 SD between remote myocardium and fibrosed myocardium, rather than other methods such as >2 SD or the "full width-half-max" (FWHM) method. A level of >5 SD has been shown to be more accurate than 2 SD and as accurate as FWHM for quantification of fibrosis by LGE (31). Quantification of LGE using manual planimetry may be a potential limitation of the study, and future techniques such as T1 mapping may overcome this.

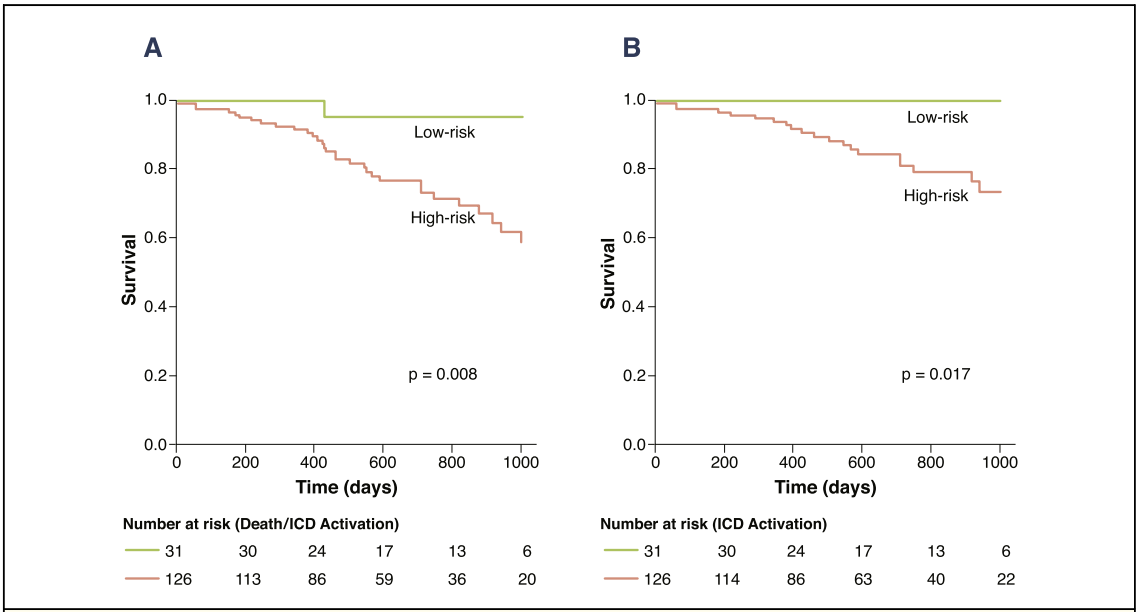

Figure 1. Survival Curves for the Population

Kaplan-Meier curves of the association between the combination of late gadolinium enhancement (LGE) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) for prediction of death or appropriate implantable cardioverter-defibrillator (ICD) activation. **(A)** Prediction of appropriate ICD activation alone. **(B)** Stratified into 2 risk groups: dilated cardiomyopathy (low-risk LGE 0%, NT-proBNP <545 pg/ml; high-risk LGE >0%, NT-proBNP ≥545 pg/ml) and ischemic cardiomyopathy (low-risk LGE <23%, NT-proBNP <848 pg/ml; high-risk LGE ≥23%, NT-proBNP ≥848 pg/ml).

CONCLUSIONS

In a real world population of patients with ICM and DCM, both percentage of LGE and NT-proBNP were associated with poorer outcome and used in combination were able to discriminate risk of death or ICD activation in patients undergoing implantation of a primary prevention ICD. The use of both markers allowed identification of a group at low risk for future adverse events in whom ICD implantation may be deferred. Larger studies should be conducted to identify the optimal levels of LGE and NT-proBNP for these markers to be incorporated into clinical guidelines.

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Key Words: natriuretic peptides ■ death ■ implantable cardioverter-defibrillator (ICD) ■ MRI.

▶ **APPENDIX**

For supplemental figures, please see the online version of this article.